

UPDATE ARTICLE

Different Uses Of Angiotensin – Converting Enzyme Inhibitors

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Summary

The renin-angiotensin-aldosterone system plays a key role in the regulation of fluid and electrolyte balance. Angiotensin-converting enzyme inhibitors (ACEIs) inhibit angiotensin-converting enzyme and have been shown to be effective in many cardiovascular diseases, including hypertension, heart failure, myocardial infarction and diabetic nephropathy. ACEIs are the most effective class of drugs in reversing left ventricular hypertrophy due to hypertension. ACEIs improve cardiac function and reduce mortality in congestive heart failure and after myocardial infarction. ACEIs should be considered in diabetics with microalbuminuria or albuminuria, especially in the presence of hypertension. There are many different ACEIs available now; they are largely similar in their effects, but differ particularly in pharmacokinetics. Choice will depend on previous experience, availability and price. There are a number of side-effects associated with ACEIs; periodic monitoring of renal function and electrolytes is required. (HK Pract 1996; 18: 398-406)

Keywords: angiotensin converting enzyme inhibitor, hypertension, myocardial infarction, heart failure, diabetic nephropathy

摘要：

在人類體液調節及電解質平衡的過程中，腎素 — 血管緊張素 — 醛固酮系統佔有一重要地位，而血管緊張素轉化酶抑制劑（ACEIs）在很多心血管疾病的治療中，包括高血壓，心力衰竭，心肌梗塞及糖尿病性腎病均有明顯效用。

現時對逆轉左心室肥大的高血壓病人，ACEIs是最有效的一類藥物。通過改善心臟功能，ACEIs可降低心力衰竭及心肌梗塞後的死亡率。當患有微蛋白尿症或白蛋白尿症的糖尿病病人並發高血壓，應考慮用ACEIs作治療。

現今市場上有多類ACEIs出售，除藥物動力學上有差異外，大多有相似作用。藥物的價錢，中用程度，醫生與病者的經驗成為選擇的主要因素。

用藥期間雖對ACEIs引發的副作用作定期腎功能及電解質的監測。

Introduction

Angiotensin-converting enzyme inhibitors (ACEI) are a class of drugs which inhibit angiotensin-converting enzyme (ACE). In the last decade, they have been shown to be effective in many cardiovascular diseases, including hypertension, heart failure, myocardial infarction and diabetic nephropathy.

Pharmacology

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the regulation of fluid and electrolyte balance (Table 1). Decreased renal perfusion pressure, as a result of hypotension for example, triggers the release of renin. Renin is a plasma enzyme which cleaves angiotensinogen to angiotensin I.

Angiotensin I is relatively inactive; its potency is increased 100-fold when it is converted to angiotensin II by ACE. Angiotensin II is a potent constrictor of vascular smooth muscle and also stimulates the synthesis and release of aldosterone from the adrenal cortex. Aldosterone acts on the distal tubules and collecting ducts of nephrons in the kidney to increase the absorption of sodium and excretion of potassium. By

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UPDATE ARTICLE

inhibiting the formation of angiotensin II, ACEIs indirectly reduce aldosterone secretion and thereby suppress the reabsorption of sodium and excretion of potassium in the distal tubule.

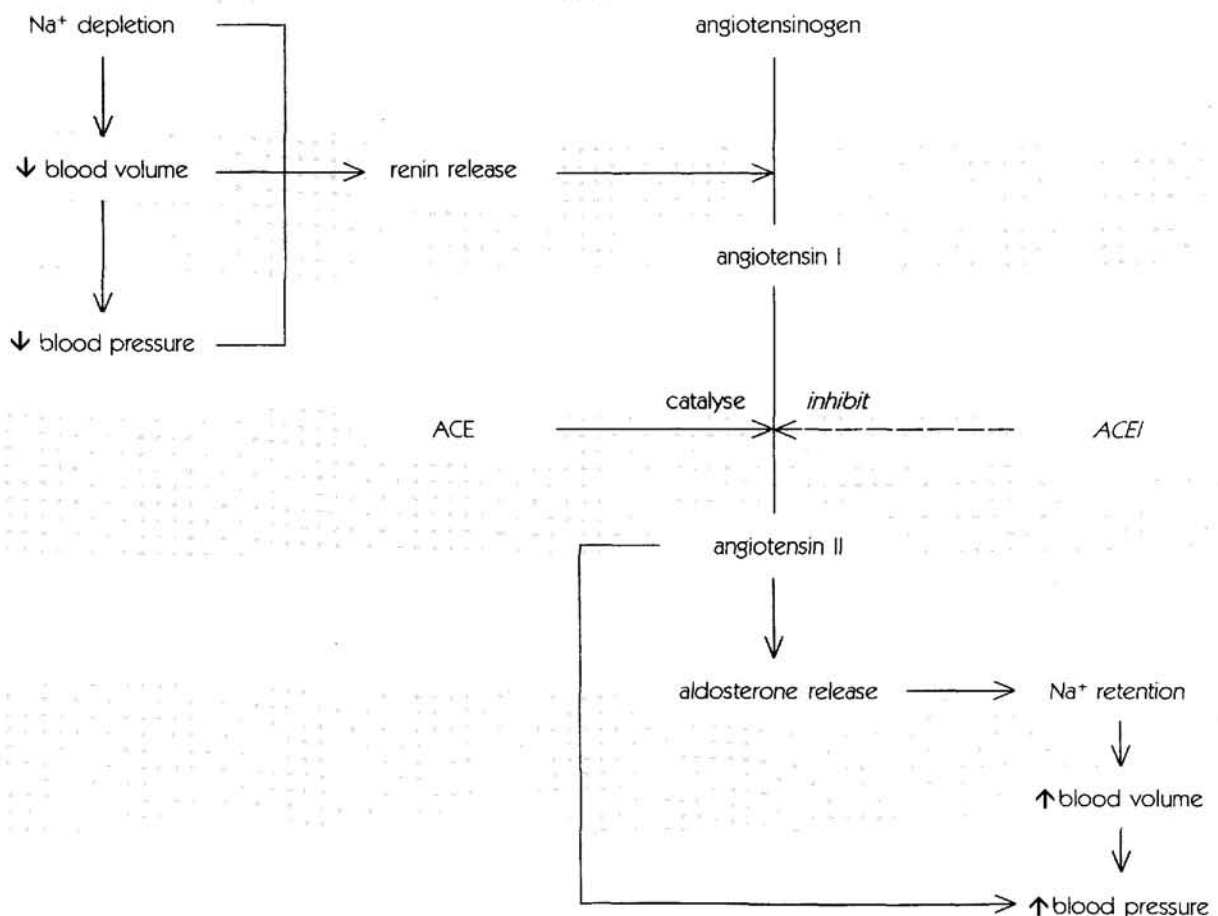
In addition to the effect on the RAAS, ACEIs have other effects. ACE has been described as a promiscuous enzyme because, beside converting angiotensin I to angiotensin II, it also catalyses other substrates including the kinins.^{1,2} Whilst angiotensin I is converted to the more active angiotensin II by ACE, bradykinin is inactivated by ACE. Hence, blocking

ACE increases bradykinin. Whether this accounts for part of the effects of ACEI and whether the potentiation of bradykinin is beneficial or not is unclear, and more studies are needed to clarify this.

There are now more than half a dozen ACEIs available (Table 2). They are largely similar in terms of their effects, but differ in several respects, particularly in pharmacokinetics. Captopril, which was the first ACEI developed, has a relatively short half-life, necessitating two or three times a day dosages. The newer ACEIs tend to have longer half-lives

allowing once-daily dosage. Some of the new ACEIs, such as fosinopril, are metabolised by the liver as well as excreted by the kidneys.³ This dual route of excretion may be an advantage in patients who have impaired renal function including for example, the elderly. ACEIs also differ in the extent of tissue binding. It is now known that apart from circulating angiotensin II, angiotensin II is also generated in tissues by tissue ACE. It is possible that the proliferative effects of angiotensin II in tissues may be better blocked by ACEIs which achieve higher concentrations in the tissues.

Table 1: A simplified diagram illustrating the role of the renin-angiotensin-aldosterone system in sodium and volume homeostasis



UPDATE ARTICLE

Table 2: ACE inhibitors currently available in Hong Kong

Drug Name	Trade Name	Dosage		Comments	Major Trials
		Hypertension	Heart Failure		
captopril	Capoten	12.5 mg bd–50 mg td	6.25 mg td–50 mg td	short-acting	SAVE, ¹⁹ ISIS-4 ²²
cilazapril	Inhibace	1 mg od–5 mg od			
enalapril	Renitec	5–20 mg od	5–20 mg od-bd	not a true once-daily drug	CONSENSUS, ¹⁵ V-HeFT II, ¹⁶ SOLVD ¹⁷
fosinopril	Monopril	10–40 mg od		hepatic and renal route of elimination	
lisinopril	Zestril	2.5–20 mg od	2.5–20 mg od		GISSI-3 ²¹
perindopril	Acertil	2–8 mg od	2–8 mg od	1st dose hypotension less likely	
quinapril	Accupril	2.5–20 mg od-bd	2.5–20 mg od-bd		
ramipril	Tritace	1.25–10 mg od	1.25–5 mg bd		

Some ACEIs are claimed to cause less side-effects. For example, first-dose hypotension is rare with perindopril while fosinopril is thought to cause less cough.^{4,5} Whilst these claims are interesting, the scientific basis of these differences have not been elucidated.

Adverse effects of ACEI

Since ACEIs inhibit the release of aldosterone, they decrease the sodium/potassium exchange in the distal renal tubules and potassium retention tends to occur. Hyperkalaemia is therefore a common side-effect of ACEIs (Table 3). It is especially likely in patients with poor baseline renal function. Since it is a well recognised side-effect, most physicians will take the precaution of not prescribing potassium supplement, nor potassium-sparing diuretics such as amiloride or spironolactone concurrently.

As the RAAS is activated when a person is volume or salt depleted, ACEIs may induce in such individuals postural hypotension, especially after the first dose. This phenomenon has been termed “first-dose hypotension” and is also a well recognised side-effect. Therefore, in patients who may be affected by first-dose hypotension, such as those patients with severe heart failure already receiving high-dose diuretics, those whose blood pressure is already low, and elderly patients, ACEI should be initiated very carefully, usually under close medical supervision in hospital. In such patients, diuretics would be reduced in dosage or stopped, and any hypovolaemia corrected. Then, the lowest dose of an ACEI, such as captopril 6.25 mg, would be started with the patient recumbent, with frequent blood pressure measurements for the first few hours.

In patients who are less likely to suffer from first-dose hypotension, precautions should still be taken. It is customary to request the patient to

take the first dose at night as they are about to retire. One of the new ACEIs, perindopril, is thought to have a much lower incidence of first-dose hypotension. The reason for this is unclear.

ACEIs should be used cautiously in patients with renal impairment for two reasons. Firstly, most ACEIs are excreted by the kidneys and therefore the plasma drug levels will be higher in patients with pre-existing renal disease. Secondly, ACEIs can sometimes worsen renal function, particularly in patients with bilateral renal artery stenosis or stenosis in the renal artery of a single functioning kidney. Some young hypertensive patients have bilateral renal arteries stenosis due to fibromuscular hyperplasia, while in the elderly, the renal arteries may be narrowed by atherosclerosis. Hence, it is customary to be cautious when prescribing ACEIs in patients with peripheral vascular disease as they

(Continued on page 402)

UPDATE ARTICLE

may have silent renovascular disease. Any sudden change in renal function after the initiation of an ACEI in such patients should alert the clinician to this possibility.

The renal toxicity of ACEI is exacerbated as expected when other nephrotoxic drugs are prescribed concurrently. For example, NSAIDs should be used with caution in a patient who is already taking ACEI. ACEIs tend to reduce renal excretion of lithium and may cause toxic plasma levels of lithium. Although ACEIs may worsen renal function or cause dangerous hyperkalaemia in patients with renal failure, nephrologists do use ACEIs in early renal failure to retard disease progression.⁶ In particular, they have been shown to slow the deterioration in renal function in diabetic nephropathy.⁷ ACEI should be used with specialist advice in these patients.

None of the ACEIs have been tested in human pregnancy and therefore this class of drugs should not be used in pregnancy. Methyldopa (Aldomet) remains the drug of choice for hypertension in pregnancy.

Captopril used at high doses has been associated with rare cases of thrombocytopenia, neutropenia and agranulocytosis. This is thought to be related to the sulphhydryl group, so other ACEIs may not share this problem. ACEIs may depress erythropoiesis, which is especially a problem in patients with chronic renal failure. ACEIs sometimes cause hypersensitivity reactions, rash, urticaria and angioneurotic oedema. In such patients, ACEIs are contraindicated.

A common and important problem is that a proportion of patients suffer from ACEI-induced troublesome dry cough. This side-effect may be caused by potentiation of kinins. The cough tends to occur in women and at night. It does not respond to cough mixtures and anti-histamines, and

frequently necessitates a reduction in dosage or withdrawal of the drug. It has been suggested that the incidence of dry cough is particularly high in Hong Kong Chinese. The authors' approach is to ascertain that the cough is related to ACEI in the first place. Sometimes, a careful history would reveal that the cough is due to some other reasons such as common cold, chest infection or worsening heart failure. There is little evidence that cough mixtures that are commonly prescribed work, but there is no harm in trying them. Then, the indications for ACEI would be reviewed. If the patient has heart failure (e.g. ejection fraction 35% or less) or diabetic nephropathy, the case for continuing the ACEI is strong. Otherwise, the ACEI should be changed to another class of drugs. In those patients who require ACEI despite cough, it is worth trying inhaled sodium cromoglycate, which is normally used for asthma. This treatment is not harmful and there is some evidence from small trials that it works.⁸ In future, losartan, an angiotensin II receptor antagonist, may be used instead of ACEI as it does not cause cough, but its effectiveness in reducing cardiovascular mortality or retarding nephropathy needs to be established first.

Hypertension

ACEIs are effective drugs in the treatment of hypertension.⁹ They

may also have additional beneficial effects such as regression of left ventricular hypertrophy (LVH) and remodelling of blood vessels. In meta-analyses of trials investigating agents which regress LVH, ACEIs have consistently been shown to be superior to other classes of anti-hypertension drugs.¹⁰ LVH is now recognised to be the single most potent risk factor for cardiovascular events and mortality. Patients who have concomitant conditions such as diabetes, heart failure or history of MI should receive an ACEI as the first choice. Otherwise, ACEIs are currently not recommended as first-line drugs in hypertension, because unlike diuretics and beta-blockers, there are no clinical trials which have shown that an ACEI reduces cardiovascular mortality in hypertensive patients.¹¹

If one chooses an ACEI for hypertension, one should use a once-daily agent to minimise the peaks and troughs in blood pressure and to improve compliance. However, ACEIs are not uniformly effective in all individuals. The response to ACEI may have a genetic component and may also be dependent on the degree of activation of the RAAS.^{12,13} If the blood pressure response to an ACEI is unsatisfactory despite adequate dosage and compliance, another class of anti-hypertensive drugs should be considered.

Table 3: Adverse effects of ACE inhibitors

hypotension (especially following the 1st dose)
persistent dry cough
taste alteration
renal impairment
hyperkalaemia
urticaria
rashes
angioedema
hypersensitivity reactions
blood disorders (anaemia, thrombocytopenia, neutropenia, agranulocytosis)
jaundice

UPDATE ARTICLE

Heart failure

In heart failure, there is activation of the RAAS, resulting in sodium and fluid retention. This may initially be a response to low cardiac output but can be deleterious in the long run. Currently, it is believed that such neurohormonal activation in heart failure is harmful and therapy should be directed at reducing this.¹⁴ ACEIs are effective in suppressing the RAAS. Successive clinical trials such as Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),¹⁵ Vasodilator Heart Failure Trial (V-HeFT II)¹⁶ and Studies of Left Ventricular Dysfunction (SOLVD)¹⁷ have shown that ACEIs reduce mortality in heart failure (Table 4). The data are now so compelling that it is no longer thought to be ethical to withhold suitable heart failure patients from ACEI therapy. Furthermore, SOLVD showed that patients with left ventricular ejection fraction of 35% or less benefited from treatment with ACEI even if they were asymptomatic. Hence, in patients suspected to have any significant degree of left ventricular dysfunction, measurement of ejection fraction by echocardiography is necessary and is now part of the modern management of heart failure.¹⁸ As mentioned above, ACEIs should be started cautiously in heart failure patients, usually in hospital with close monitoring. The starting dose should be low and increased gradually. Diuretics should be reduced or stopped for a few days before introducing an ACEI. The optimal dose of ACEI in heart failure remains unresolved. In SOLVD, the target dose of enalapril was quite high, 20 mg daily. In practice, most physicians tend to use lower doses. It remains to be established that lower doses are as effective as high doses in reducing mortality. ACEIs, when used in conjunction with diuretics in heart failure, may cause disturbances in renal function and electrolytes, and so careful monitoring of these are essential.

Table 4: Summary of the major clinical trials investigating the effect on mortality after ACEI therapy

Trial	Subjects	Drug	Relative risk reduction (% deaths prevented)
CONSENSUS ¹⁵	CHF (NYHA Class IV)	enalapril	40 %
SOLVD ¹⁷	CHF (EF ≤ 35%)	enalapril	13 %
SAVE ¹⁹	MI (EF ≤ 40%)	captopril	19 %
AIRE ²⁰	MI with HF	ramipril	27 %
GISSI-3 ²¹	MI	lisinopril	11 %
ISIS-4 ²²	MI	captopril	9 %

Myocardial infarction

ACEI and thrombolysis represent major advances in the treatment of myocardial infarction (MI) in recent years. Large-scale studies such as Survival and Ventricular Enlargement Study (SAVE),¹⁹ Acute Infarction Ramipril Efficacy Study (AIRE),²⁰ Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3)²¹ and International Study of Infarct Survival (ISIS-4)²² all testified to the effectiveness of ACEIs in reducing long-term mortality of patients after MI and improving their cardiac function (Table 4). By influencing cardiac remodelling following MI, ACEIs help to prevent deterioration in ventricular function and development of heart failure. It is still an unresolved question as to who should receive ACEIs after MIs. Hypotension and poor renal function are relative contraindications. It seems that patients with overt heart failure²⁰ or poor ejection fractions¹⁹ would benefit most from these drugs, but all MI patients might benefit to some extent.^{21,22} However, CONSENSUS II showed that aggressive non-selective use of an ACEI (involving an intravenous first dose) immediately after acute MI may not be beneficial.²³ Although GISSI-3 and ISIS-4 both showed that oral ACEIs can be given within the first 24 hours, the magnitude of benefit was not very large, around 10% reduction

in mortality. In contrast, the reduction in mortality in the SAVE and AIRE studies were 19% and 27% respectively, largely because of selective inclusion of patients with low ejection fraction¹⁹ or overt heart failure.²⁰ Nevertheless, these two studies which randomised patients from day 3 onwards after MI indicated that the ACEI does not need to be started within the first 24 hours. The authors' view is that it is not worth subjecting a haemodynamically unstable patient after acute MI to ACEI within the first 24 hours when the benefits are so modest and when the probability of hypotension is high (20% in ISIS-4)²². The decision to start ACEI can be made when a patient is stabilised.

Diabetes

A pioneering study by Lewis and colleagues showed that captopril prevented the progression of diabetic nephropathy.⁷ The outcome measures were doubling of serum creatinine or progression to dialysis or transplantation. Other studies showed that ACEIs prevent the progression from microalbuminuria to albuminuria.²⁴ Microalbuminuria (albumin excretion 30-300 mg/24hr) is an early marker for deterioration in renal function, and is often present 10 years after the onset of diabetes.

(Continued on page 405)

UPDATE ARTICLE

Currently, it is thought that diabetics with microalbuminuria or albuminuria should receive an ACEI, especially in the presence of hypertension. To identify diabetic patients with microalbuminuria, either a spot urine specimen, 12-hour overnight urine collection or 24-hour urine collection should be sent to the laboratory as urine dipsticks are not sensitive enough. We favour 24-hour urine collection as creatinine clearance can be determined at the same time.

Other beneficial effects

ACEIs may have other beneficial effects, such as improving endothelial dysfunction. The on-going Trial on Reversing ENdothelial Dysfunction (TREND) study is investigating if quinapril restores the reactivity of vascular muscle to vasodilating agents in coronary arteries. ACEIs may also reduce the thickness of arterial walls and restore arterial compliance.^{25,26}

Choice of ACEIs

There are now numerous ACEIs on the market. Choice will depend on prior experience of a particular drug, availability and price. Captopril is often used as the test dose when ACEI therapy is started because it is short-acting and so adverse effects would be comparatively short-lived. For long term use, a long-acting drug has the theoretical advantage of once-daily dosage to improve compliance and smoother plasma levels. If first dose hypotension or renal impairment is a concern, then perindopril or fosinopril respectively may be preferred. In using some of the latest ACEIs, one is of course extrapolating from clinical trials in which a different ACEI might have been used, but the evidence so far suggests that the benefits in heart failure and MI are class effects.

Losartan

Losartan, an angiotensin II antagonist, is a new class of drug which has recently been launched world-wide.²⁷ It acts in a different manner to ACEIs in that it blocks the binding of angiotensin II to one of its receptors. This may result in a more complete blockade of the cardiovascular effects of angiotensin II. Moreover, losartan does not cause cough and first dose hypotension.²⁸ Nevertheless, there are two reasons why losartan should be used with reservation at this stage. Firstly, it is a new drug and there are no long term studies showing any benefit in terms of reduction of mortality in hypertension, heart failure or MI. Secondly, ACEIs block not only the RAAS but also enhance the formation of kinins. There are animal data to suggest that some of the beneficial effects of ACEI are brought about by changes in the kinin system.² Losartan will have no direct effect on the kinin system and therefore may not reproduce all the benefits of ACEIs.

Conclusion

ACEIs have established an enviable reputation, especially in the treatment of heart failure and MI. There are many potential problems and side-effects associated with ACEIs, and patients taking ACEIs may require periodic monitoring of renal function and electrolytes. However, large clinical trials have established clearly the usefulness of ACEIs in heart failure, MI and diabetic nephropathy, so they have an important place in the formulary.

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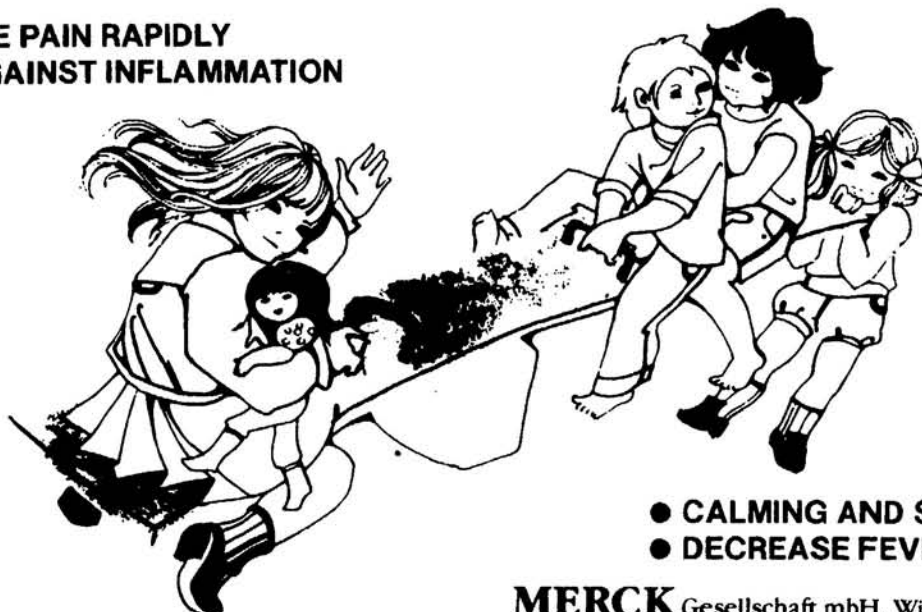
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